The out-of-focus bias in drug surveillance

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Abstract: PURPOSE: Existing drug safety systems with phase II and III studies and post-marketing surveillance by principle do not allow for the recognition of an important class of adverse drug reactions (ADRs). ADRs that are resistant to being detected reliably may a) appear as if they are age-related chronic diseases, which also manifest themselves in a high degree without drug treatment, b) arise in "old" drugs, c) arise during long-term application, and d) arise with the administration to frail and aged populations. CONCLUSIONS: "Silent" and multi-factorial health problems evolving from long-term drug treatment must therefore be addressed with a systematic search strategy, as a third track along with the phase II and III studies and spontaneous reporting systems which still exist.

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The out-of-focus bias in drug surveillance

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Summary
Existing drug safety systems with phase II and III studies and post-marketing surveillance do not allow recognizing an important class of adverse drug reactions (ADRs) by principle. ADRs which are resistant to being detected reliably may a) be appearing like and age-related chronic diseases which also manifest themselves in a high degree without drug treatment, b) arriving in "old" drugs, c) during long-term application, and d) with the administration to frail and aged populations. "Silent" and multi-factorial health problems evolving from long-term drug treatment must therefore be addressed with a systematic search strategy, as a third track along with the phase II and III studies and spontaneous reporting systems which still exist.

Existing pharmacovigilance system and its limitations

The path to our drug surveillance system has been a thorny one [1]. In the USA, the FDA was only allowed after 1938 to demand safety documentation of drugs, and only in 1962, manufacturers could be required to prove the effectiveness of their drugs. Newer developments include the opportunity to ask drug safety questions electronically in the Sentinel system which encompasses up to 100 million patient records [2]. Nevertheless, pre- and especially post-marketing drug surveillance may have some systematic pitfalls. When testing new drugs in phase II and III studies, all aspects of their desired outcomes are investigated. In order to register adverse drug reactions (ADRs), some laboratory tests will be conducted and patients are either asked via a checklist of defined questions, or their complaints are registered when they are expressed spontaneously. If a drug belongs to a certain therapeutic class, its assumed ADRs are routinely checked. ADRs other than those that are expected may be discovered by mere chance. Post-marketing studies are designed to detect rare or late-emerging ADRs, but they will be performed only to verify signals of spontaneous reporting systems (SRS). Thus, after entry to the market (phase IV), no more systematic searches for ADRs will be made.

Blind spots

Chronic health problems are frequently found in elderly patients – therefore it's virtually impossible to differentiate an increased proportion of a certain chronic illness from the "frog perspective" by a single physician as an ADR occurring only after years of treatment. For example, an increased probability of 20% of diabetes type 2 resulting in one out of four instead of one out of five persons becoming diabetic during a ten-year treatment of hypertension with thiazide diuretics would be a relevant health problem, but could only be detected by systematically searching for it and not by SRSs. Many chronic health disturbances are associated with long-term medication. Examples which are known include ocular cataracts (steroids), osteoporosis (glitazones), myocardial infarction (non-steroidal anti-inflammatory drugs), vitamin B12 deficiency (metformin), vitamin D deficiency (antiepileptics) and so on.

Out of sight – out of mind!

Practical examples

Recently we noted that calcium supplements might raise the risk of myocardial infarction (MI); the association was detected by chance in two meta-analyses and confirmed in a large cohort study [3]. An MI in a patient taking supplements for five to ten years would normally not be attributed to the long-term use of these bone-protecting pills, and therefore the association cannot be detected by SRSs. Our point is not whether or not calcium supplements really cause myocardial infarction [4], but even if this was the case, existing drug surveillance would probably miss detecting it by SRS. On the other hand, epidemiological studies not prospectively designed to detect specific ADRs (here, MIs as a function of calcium supplement intake) can always be criticized and their results judged to be inconclusive.

Let us take a look at another example. Last year we published a review article on osteoporosis in Parkinson's disease patients and its possible cause or worsening by antiparkinsonian treatments [5]. The conclusion was that there is a strong and reliable association between osteoporosis and either Parkinson's disease or antiparkinsonian treatments containing L-dopa.

We contacted the manufacturers of Madopar® and Sinemet® in order to inform patients that these drugs might be associated with negative aspects of bone metabolism. But neither Roche, the MSD companies, nor our Swiss drug authority (Swissmedic) accepted our suggestion to include this in the medical consumer information. The reasons were: A) "We think that Parkinson's osteoporosis is caused by the disease itself or by concomitant sequelae like vitamin D and protein deficiency and immobility." B) "We cannot have Swiss 'run alones' in product information." C) "There are no SRS signals of that coincidence."

In the case of Parkinson's osteoporosis, there was no information set in stone about a causal relationship with L-dopa. But when warning people of a danger that could be avoided, does it make a difference whether the obvious red flag (L-dopa treatment) is the cause, or only a marker of the imminent damage? We think that it doesn't, at least for patients and their doctors! Are the SRS reports that are lacking an absolution for L-dopa treatment? Parkinson's patients are chronically ill. Damage to bones will develop over several years. If a patient breaks his hip after ten years of antiparkinsonian treatment, nobody will think that this multi-factorial event was caused or worsened by drug treatment. But this would be the case even if there was a strong but hidden influence by using drugs containing L-dopa, and so, the missing SRS notifications are without any proven value for drug safety.

Indeed there is a clear metabolic pathway of L-dopa metabolized to homocysteine (especially in patients with genetic abnormalities like C677T or E1298A of methylenetetrahydrofolate-reductase, but also in others), raising serum levels by one- or twofold over the upper normal value. And there is clear evidence that very high homocysteine levels lead to bone loss [6, 7]. But there are no placebo controlled randomized studies for this issue because it is ethically not feasible to withhold L-dopa from Parkinson's patients.

When informing patients and their physicians, drug authorities and companies could contribute to minimizing an avoidable health problem because for the physicians there are easy prevention measures, such as starting treatment with dopamine-agonists instead L-dopa, avoiding high doses of L-dopa, early addition of a COMT-inhibitor to L-dopa, deliberate substitution with vitamin D, B_6 and B_{12} as well as folic acid, and also blocking bone degradation with a bisphosphonate or denosumab (although both may also cause ADRs).

Reasons why things are not changing

Are randomized controlled trials needed in this area [8]? In the case of L-dopa, there is little hope that trials will be ever made. For other drugs emerging in the long-term treatment market, observational studies should routinely be performed, comparing group illness with standardized disease rates. These studies will not have the same evidence as randomized controlled trials, but they are the only way to get information where placebo-controlled trials are not feasible.

Among the blind, the one-eyed man is king.

Will treatments which were recently accepted do any better than L-dopa? Probably not! Rivaroxaban (Xarelto®) is now registered for anticoagulant treatment in chronic atrial fibrillation. Solayar et al published an *in vitro* study about depressed osteoblast activity in the presence of rivaroxaban [7]. Currently no ongoing clinical studies (ClinicalTrials.gov and as admitted by the Bayer Company) are investigating bone health in long-term treatment with rivaroxaban.

"Silent" and multi-factorial health problems evolving in long-term treatment must be addressed with a systematic search strategy. Large cohort studies will only detect what is within the focus of the study. SRSs will not help either, because the coincidences of drug treatment with a given health disturbance are often not evident to the caregivers (and filling in the SRS forms is not their favorite pastime). On average, SRSs suffer from overwhelming rates of under-reporting of 94% (median value), and selective reporting also seems to happen frequently [10-12]. Hence, the real proportion of under-reporting of ADRs could even be higher since the denominator of the studies was the total of all "known, suspected or expected" ADRs after tiny controls of the patient charts; but unsuspected, e.g. cases of MI during treatment with calcium supplements or hip fractures in patients taking L-dopa were not counted as ADRs which were missing. Because of the eminent rates of underreporting, the suspected selective reporting and the unspectacular appearance of many ADRs, inferences changing only proportions of disease rates are seldom detectable by SMRs. We do not wish to underrate the important contributions of SRS to drug surveillance [13], but their obvious limitations should be made evident to every prescriber of drugs.

New focus in pharmacovigilance

In our opinion, there are several factors which favor under-reporting or selective reporting of ADRs (Table 1). Systematic reporting may be mainly precluded by a high prevalence of and an alternate explication for an alleged ADR. Therefore, fractures and osteoporosis should be systematically considered when introducing a new drug for long-term use to the market. The latter can easily be monitored by measuring mineralized bone density as well as pyridinoline crosslinks in urine. Focus should also be on patient survival, heart attacks and strokes, dementia, diabetes, hypertension, renal insufficiency, cancer, and macular degeneration. Special situations continue to be treatment applications for children and pregnant women.

Table 1. Factors contributing to under-reporting of ADRs

- high prevalence of the problem also in patients without administration of the drug
- insidious, unspectacular appearance of age-related chronic disease
- resulting from the use of "old" drugs
- long-term application
- administration to frail and aged populations [14]
- presence of alternate explications

We need a systematical observational post-marketing program to improve our patchy reporting system to detect previously unknown ADRs in long-term drug treatment. Health care professionals should be sensitized to detect ADRs and encouraged to report them to their authorities to uncover serious adverse events and therefore prevent harming their patients. A lack of opportunity to perform randomized controlled trials should not be a reason to allow manufacturers to lose focus on the long-term safety of their drugs.

It seems that there is a lot of work to do. Let's get the focus right!

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